Autosomal Dominant and Recessive Inheritance

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Introduction

- diseases result from mutation of a single gene
- 1994 - MIM-McKusick - 6678 monogenic traits
  - 6178 - autosomes
  - 412 - sex chromosomes
- patterns of inheritance
- factors that complicate this pattern
- molecular basis if known

Topics of Discussion

- Basic concepts of formal genetics
- Autosomal dominant inheritance
- Autosomal recessive inheritance
- Factors that may complicate inheritance patterns
- Probability

Topics of Discussion

- Basic concepts of formal genetics
- Gregor Mendel's contributions
  - principle of segregation
  - principle of independent assortment
- Basic principles of probability
- Gene and genotype frequencies
- Hardy-Weinberg Principle
- Concept of phenotype
- Basic pedigree structure

Principle of Segregation

- sexually reproducing organisms produce genes that occur in pairs
- only one member of this pair is transmitted to offspring (i.e. it segregates)
- prevalent thinking during Mendel's time was that hereditary factors from the two parents "blended" in the offspring
- In fact - genes remain intact and distinct
- key to modern genetics

Principle of Independent Assortment

- Genes at different loci are transmitted independently
- Consider two loci - *rounded* or *wrinkled* at one, *tall* or *short* at other
- In a reproductive event a parent will transmit one allele from each locus to its offspring
- the allele transmitted at one locus (*r* or *w*) will have no effect on the other locus (*t or s*)

Dominant or Recessive

- Mendel's work also demonstrated that effects of one allele may mask those of another
- Crosses between pea plants homozygous for "tall" gene (*H*) with those homozygous for "short" gene (*h*)
- This cross produces only heterozygotes (*Hh*)
- Offspring of these crosses were all tall even though heterozygous
- *H* allele is dominant whereas the *h* allele is recessive
- recessive comes from the Latin root - "to hide"

Basic Probability - Summary

- Allows us to understand and estimate genetic risks
- Multiplication rule is used to estimate the probability that two events will occur together
- Addition rule is used to estimate the probability that one event or another occurs

Genes and Genotype Frequencies

- Specify the proportions of each allele and each genotype, respectively in a population
- Under simple conditions, these frequencies can be estimated by direct counting

Hardy - Weinberg Principle

- Frequency of Genes:
  - p = frequency of normal allele
  - q = frequency of mutant allele
  - p + q =1

Hardy - Weinberg Principle

- $p^2 + 2pq + q^2 = 1$ and $(p + q = 1)^2$
- p^2 = frequency of homozygous normal
- $2pq$ = frequency of heterozygotes
- q^2 = frequency of homozygote abnormal

Hardy - Weinberg Principle

- if given pop frequency of an AR disorder = 1/2500 (CF)
- then $q^2 = 1/2500$, and $q = 1/50 = 0.02$
- $p + q = 1$ therefore $p = 0.98$ (almost 1)
- Heterozygous carriers = $2pq = 1/25$
- Incidence of homozygous affected is low (1/2500), the heterozygote frequency is more common 1/25

H-W - Risk Calculation

- For man who has a sibling with AR condition he has 2/3 chance of being heterozygous carrier
- Unrelated woman in pop has risk of 1/25 (gene frequency) of having one abnormal gene
- they have 1/4 chance of having a homozygous affected child
- 2/3 x 1/25 x 1/4 = 2/300 = 1/150

Hardy - Weinberg Principle

- Under panmixix, the H-W principle specifies the relationship between gene frequencies and genotype frequencies
- Useful in estimating gene frequencies from disease prevalence data
- Useful in estimating the incidence of heterozygote carriers of recessive disease genes

Concept of Phenotype

- Genotype - individual's genetic constitution at a locus
- Phenotype - is what we actually observe physically or clinically
- Genotypes do not uniquely correspond to phenotypes
- Two different genotypes, a dominant homozygote and a heterozygote may have the same phenotype - i.e. CF

Concept of Phenotype

- Same genotype may produce different phenotypes in different environments
- recessive disease phenylketonuria (PKU) seen in about 1 in 10,000 white births
- Mutations for gene encoding enzyme phenylalanine hydroxylase - unable to metabolize phenylalanine
- PKU babies on average lose 1-2 IQ points per week during first year of life if not treated
- Low Phenylalanine diet within 1 month of birth leads to normal IQ and development!!

Basic Pedigree Structure

- one of most commonly used tools in medical genetics
- illustrates the relationship among family members
- shows which family members are affected with genetic disease and which are unaffected
- an arrow denotes the **proband**, the first individual diagnosed in the pedigree (**index case, propositus**)

Autosomal Dominant Inheritance

- More than 3700 AD traits (mostly diseases) known
- Each rather rare in population - common ones with gene frequencies of about 0.001
- Matings between two individuals with same AD disease are uncommon
- Most often affected offspring are produced by union between affected heterozygote and a normal parent

Autosomal Dominant Inheritance

- Punnett square shows that affected parent either passes a normal or disease gene to the offspring
- Each event has a probability of 0.5
- Thus, on average, half of the children will be heterozygous and express the disease and half will not

Autosomal Dominant Inheritance

- Postaxial polydactaly, the presence of an extra digit next to the fifth digit can be inherited as an AD trait
- If “A” symbolizes the gene for polydactaly, and “a” the normal gene, the pedigree below will demonstrate important characteristics of AD inheritance

Autosomal Dominant Inheritance

- Females and males exhibit the trait in approximately equal proportions
- Males and females are equally likely to transmit trait to their offspring
- No skipping of generations: if an individual has polydactaly, one parent must also have it
- Vertical transmission pattern - disease phenotype is usually seen in one generation after another
- If neither parent has the trait, none of the children has it
- Father to son transmission may be observed

Autosomal Dominant Inheritance

- vertical transmission of the disease phenotype
- lack of skipped generations
- roughly equal numbers of affected males and females
- Father-son transmission may be observed

AD Inheritance - Recurrence Risk

- Probability that subsequent children will be born with same disease
- Each birth is an independent event, as in coin-tossing example
- Recurrence risk - 1/2 or 50%
- regardless of how many affected or unaffected children are born

Autosomal Recessive Inheritance

- Fairly rare in populations
- Heterozygous carriers for recessive genes are much more common than affected homozygotes
- Parents of affected heterozygotes are usually heterozygous carriers
- Punnett square demonstrates that 1/4 of offspring will be normal homozygotes, 1/2 will be normal carrier heterozygotes, and 1/4 will be homozygous affected

Autosomal Recessive Inheritance

- A Typical example - Hurler syndrome - rare AR disorder
- resulting from a deficiency of the lysosomal enzyme, alpha-L-iduronidase
- buildup of mucopolysaccharides in lysosomes
  - skeletal abnormalities
  - mental retardation
  - coarse facial features

AR Inheritance - Pedigree

- AR diseases are usually seen in one or more siblings but not in earlier generations
- Females and males are affected in equal proportions
- 1/4 of the offspring of two heterozygous carriers will be affected with the disorder
- Consanguinity is present more often in pedigrees involving AR inheritance than with other types of inheritance

“Dominant” versus “Recessive”: Some cautions

- Dominant diseases are usually more severe in affected homozygotes than in heterozygotes
  - Achondroplastic dwarfs - heterozygotes have almost normal life span
  - Homozygotes are severely affected and usually die in infancy of respiratory failure
- Heterozygous recessive carriers can often be diagnosed because of reduced enzyme activity

Factors that may complicate Inheritance Patterns

- New mutation
- Germline Mosaicism
- Delayed age of onset
- Reduced penetrance
- Variable expression
- Pleiotropy and Heterogeneity
- Genomic Imprinting
- Anticipation

New Mutation

- gene transmitted by one of the parents
- underwent a change in DNA
- resulting in a mutation from a normal to a disease bearing gene

New Mutation - Example

- 7/8 of all cases of achondroplasia are due to new mutations
- 1/8 transmitted from achondroplastic parents
- must know adequate family history to distinguish

New Mutation

- Frequent cause of appearance of genetic disease in individual with no prior family history of disorder
- recurrence risk for individual's siblings is very low
- may be substantially elevated for individual's offspring

Germline Mosaicism

- occurs when all or part of a parent's germline is affected by a disease mutation
- but somatic cells are NOT affected
- elevates recurrence risk for future offspring of mosaic parent

Germline Mosaicism

- Two or more offspring will present with an AD disease when there is no family history of disease
- Because mutation is rare event, it is unlikely that this would be due to multiple mutations in the same family
- Mosaic is an individual who has more than one genetically distinct cell lines in his or her body

Germline Mosaicism - Diseases Identified

- Osteogenesis Imperfecta - OI type II
  - lethal perinatal form
- Achondroplasia
- Duchennes Muscular Dystrophy
- Hemophilia A

Delayed Age of Onset

- Can cause difficulty in deducing mode of inheritance
- not possible until later in life to determine whether an individual carries a mutation
- Some examples include:
  - Huntington Disease
  - Polycystic kidney disease
  - Hemochromatosis
  - Familial Alzheimer disease
  - AD form of breast cancer

Reduced Penetrance

- an individual who has the genotype for a disease may not exhibit the disease phenotype at all, even though he or she can transmit the disease gene to the next generation
- Retinoblastoma - AD malignant eye tumor is a good example of reduced penetrance
- About 10% of the **obligate carriers** of the RB susceptibility gene (affected parent and affected child or children) ***do not have the disease***

Variable Expression

- Penetrance may be complete, but severity of disease can vary greatly
- Well-studied example is neurofibromatosis type 1, or von Recklinghausen disease (named after the German physician who described it in 1882)
- Parent with mild expression of disease (so mild they may not know they carry gene), can transmit gene to child who can have severe expression
- Provides a mechanism for disease genes to survive at higher frequencies in populations

Variable Expression - Causes

- Environmental factors
  - in absence of environmnental factor, gene is expressed with diminished severity or not at all
- Modifier genes
  - interaction of other genes
- Allelic heterogeneity
  - *B*-globin mutations that can cause sickle cell disease or various *B*-thalassemias

Pleiotropy

- Genes that exert effects on multiple aspects of physiology or anatomy are pleiotropic
- Common feature of human genes
- Good example is gene for Marfan syndrome
  - AD condition - fibrillin - chromosome 15q
  - 1896 Antoine Marfan - French pediatrician
- Affects the eye, the skeleton and the cardiovascular system

Pleiotropy

- Cystic fibrosis
  - sweat glands, lungs, pancreas, GU system
- OI
  - bones, teeth, sclera affected
- Sickle cell anemia
  - erythocytes, bone and spleen affected

Locus Heterogeneity

- Disease that can be caused by mutations at different loci in different families is said to exhibit locus heterogeneity
- OI - subunits of procollagen triple helix are encoded by two genes
  - one on chr 17 and the other on chr 7
  - mutation in either of these genes can alter the structure of the collagen molecules and lead to OI
- disease states are often indistinguishable!!
- be wary of testing for the wrong mutation and offering reassurance!!

Genomic Imprinting

- Mendel - garden peas - phenotype is the same whether a given allele is inherited from the mother or the father
- In humans this principle **does NOT** always hold

Deletion of long arm chromosome 15

- if del 15q is inherited from father, the offspring manifest a disease known as Prader-Willi syndrome
  - short stature, obesity, mild to moderate MR, hypogonadism
- if del 15q is inherited from the mother, the offspring develop Angelman syndrome
  - sever MR, seizures and ataxic gait
- in most cases deletion inherited from the mother or father are indistinguishable

Genomic Imprinting

- Genes inherited from the mother, while having the same DNA sequence, differ in some other way from those of the father (the “imprint”)
- The imprint alters the activity level of genes, so del of paternally or maternally derived chromosomes may produce different phenotypes
- “Parental origin effects” - Methylation - the more methylated a gene is the *less likely* it is to be transcribed into mRNA

Anticipation

- Some genetic diseases seem to display an earlier age of onset and/or more severe expression in more recent generations
- ?artifact - better observation or diagnosis?
- Real Biological Basis! - Myotonic Dystrophy
  - AD disease which involves progressive muscular deterioration
  - most common dystrophy that affects adults
  - 1/8000 individuals
  - Mapped to chr 19 - gene recently cloned

Anticipation - Myotonic Dystrophy

- gene is expanded CTG trinucleotide repeat
- # repeats - strongly correlated with severity of disease
  - 5-30 copies - unaffected
  - 50-100 copies - mildly affected
  - 100 to several thousand - full blown MD
- # of repeats often increases with succeeding generations - WHY?
- Severe congenital form occurs only when disease gene is inherited from mother - WHY?

Trinucleotide Repeat Expansions

- Huntington - CAG
- Myotonic dystrophy - CTG
- x-linked spinal and bulbar muscular atrophy - CAG
- Spinocerebellar ataxia type I - CAG
- Fragile X syndrome (FRAXA) - CGG
- Fragile site FRAXE - CGG
- Machado-Joseph diseas - CAG
- Friedreich’s ataxia - GAA

Consanguinity

- Increases the chance that a mating couple will both carry the same disease gene
- Seen more frequently in pedigrees involving rare recessive diseases than in those involving common recessive diseases

Consanguinity

- ***About 5%*** of cases of PKU in which the carrier frequency is about 1/50 whites - due to consanguineous matings
- In Wilson disease (recessive disorder in which excess copper is retained leading to liver damage) with a carrier frequency of 1/110 - 1/160 ***about 50%*** of the cases are result of consanguineous matings

Coefficient of Relationship

- siblings share 1/2 of their genes on average
- first cousins share 1/8
- first cousins once removed share 1/16
- second cousins share 1/32